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EXAMINER	
KHARE, DEVESH	

ART UNIT	PAPER NUMBER
1623	

DATE MAILED: 12/05/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/661,386	RUBINFELD, JOSEPH	
	Examiner	Art Unit	
	Devesh Khare	1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 October 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-58* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-58* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *See Continuation Sheet*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Continuation of Attachment(s) 3). Information Disclosure Statement(s) (PTO/SB/08), Paper No(s)/Mail Date :1/11/06;8/25/05;8/23/05;01/06/04.

Applicant's election of the claims of Group I (claims 1-58) without traverse in the reply filed on 10/24/2006 is acknowledged.

Claims 59-105 have been cancelled without prejudice.

An action on the merits of claims 1-58 is contained herein below.

2. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-58 rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-20 of U.S. Patent No. 6,998,391 ('391).

Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims in each of the application and the '391 patent are directed to substantially the same subject matter, i.e., in the instant claims, the invention is claimed in terms of a method for treating a patient having a disease associated with over expression of EZH2, comprising administering to the patient a therapeutically

effective amount of a DNA methylation inhibitor, while in the '391 patent it is claimed in terms of a method for treating a patient having a disease selected from the group consisting of inflammation, benign tumors, malignant tumors, leukemia, asthma, rhinitis, autoimmune diseases and mastolocytosis comprising administering to patient decitabine and a tyrosine kinase inhibitor. It is noted that the instant specification discloses that cancer diseases are associated with over expression of EZH2 (page 5, [0018]) and decitabine is disclosed as a DNA methylation inhibitor (specification page 8, [0034]). The '391 patent discloses that a DNA methylation inhibitor can reactivate certain genes which participate in the pathways of protein tyrosine kinase (col.8, lines 47-49) and co-administration of DNA methylation inhibitor with other inhibitors may be advantageous in the treatment of cancers (col.19, lines 30-35). Those of skill in this art would have recognized that a therapeutically effective amount of DNA methylation inhibitor alone or in combination with other inhibitors of instant claims 35,36 or 48 can be used in the treatment of various cancers. It would have been obvious to one having ordinary skill in this art, at the time the claimed invention was made to use the method of the '391 patent which is drawn in terms of a method for treating a patient having a disease selected from the group consisting of inflammation, benign tumors, malignant tumors, leukemia, asthma, rhinitis, autoimmune diseases and mastolocytosis comprising administering to patient a DNA methylation inhibitor, decitabine and a tyrosine kinase inhibitor. One of ordinary skill in the art would be motivated to use DNA methylation inhibitor alone or in combination with other inhibitors since the beneficial effects of said DNA methylation inhibitor is individually taught in the prior art.

The examiner notes the instant claims and the **'391 patent** of applicants do indeed substantially overlap therefore this obviousness-type double patenting rejection is necessary to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. Therefore the claims are co-extensive.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-58 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in **scope** with the claim with respect to treating **any** disease associated with over-expression of EZH2 in a patient broadly, and/or those numerous cancers listed in claims 7-9.

Note that **any** disease associated with over-expression of EZH2 would reasonably broadly encompass those known and unknown cancers as of the instant filing date, as well as those future known cancers yet to be discovered and diagnosed.

The instant specification fails to provide information that would allow the skilled artisan to fully practice the instant invention without ***undue experimentation***. Attention is directed to *In re Wands*, 8 USPQ2d 1400 (CAFC 1988) at 1404 where the court set forth the eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing *Ex parte Forman*, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors:

(1) the nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

1. The nature of the invention: The instant invention pertains in terms of a method for treating a patient having a disease associated with over expression of EZH2, comprising administering to the patient a therapeutically effective amount of a DNA methylation inhibitor.
2. The state of the prior art: The skilled artisan would view cancers as a group of maladies (cancers) not treatable with one medicament or therapeutic regimen. Treatment efforts and efforts to cure all cancers have produced only isolated identifiable positive results. See *In re Application of Hozumi et al.*, 226 USPQ 353. Moreover, it is well known that so far no single chemotherapeutic agent has been found to be useful in the treatment of **all** cancers, or even useful in the treatment of all types of breast cancers; and colon cancers; and prostate cancers; and leukemias. For example, breast cancers and leukemia do not share a common cause and differ

in their methods of treatment, i.e., breast cancers are routinely with estrogens, antiestrogens, and/or androgens, unlike leukemia which is routinely treated with l-asparaginase, daunorubicin, and purine analogs.

3. The predictability of the art, and the breadth of the claims: Note that the pharmaceutical art is unpredictable, requiring each embodiment to be individually assessed for physiological activity. *In re Fisher*, 166 USPQ 18 indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. Moreover, it is known that repeated therapeutic failures, after promising in-vitro test results, suggest to the skilled artisan that claims based on in-vitro data, directed to treating cancer generally, are highly unpredictable, as taught in Trisha Gura's article in *Science*, November, 1997 (PTO-892):

"[T]he institute started by pulling together mouse models of three tumors: a leukemia, which affects blood cells; a sarcoma, which arise in bone, muscle, or connective tissue; and carcinoma, the most common cells and includes such major killers as breast, colon, and lung cancers. Initially, many of the agents tested in these models appeared to do well. However, most worked against blood cancers such as leukemia and lymphoma, as opposed to the more common solid tumors. And when tested in human cancer patients, most of these compounds failed to live up to their early promise." (emphasis added, see for example, the middle column of the article).

Based on the known teachings of the cancer treatment such as in Trisha Gura's reference, one of skill in the art would recognize that it is highly unpredictable in regard to the treatment in the instant case, including treating numerous and various cancers: chronic leukemia, ovarian carcinomas, prostate cancer, bladder cancer, ovarian carcinomas, stomach cancer, rectal cancer, pancreatic cancer, throat cancer, sarcoma,

gastrointestinal cancer, breast cancer, melanoma, acute and Kaposi's sarcoma by administering the very same DNA methylation inhibitor.

4. The presence or absence of working examples: There are no working examples in the instant specification. As such, a skilled artisan would not recognize that a DNA methylation inhibitor alone or in combination with a histone deacetylase inhibitor; an EZH2 antagonist; and an anti-neoplastic agent is useful in the treatment of a disease associated with over expression of EZH2. The evidence in the specification is **not** commensurate in **scope** with the claimed invention and does not demonstrate criticality of a claimed DNA methylation inhibitor and numerous and various cancers in the claimed method. See MPEP § 716.02(d).

Further, those unknown or future known cancers must require additional or future research to discover and diagnose. Therefore, the skilled artisan has to exercise **undue experimentation** to practice the instant invention.

Thus, the specification fails to provide sufficient support of the broad use of said DNA methylation inhibitor alone or in combination with a histone deacetylase inhibitor; an EZH2 antagonist; and an anti-neoplastic agent for treating numerous and various cancers recited in the instant claims. As a result, necessitating one of skill to perform an exhaustive search for a DNA methylation inhibitor alone or in combination with a histone deacetylase inhibitor; an EZH2 antagonist; and an anti-neoplastic agent and cancers encompassed by the instant claims suitable to practice the claimed invention.

Genentech, 108 F.3d at 1366, states that "a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion" and "[p]atent

protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable".

Therefore, in view of the *Wands* factor and *In re Fisher* (CCPA 1970) discussed above, to practice the claimed invention herein, a person of skill in the art would have to engage in *undue experimentation* to test a DNA methylation inhibitor alone or in combination with a histone deacetylase inhibitor; an EZH2 antagonist; and an anti-neoplastic agent and cancers encompassed in the instant claims, with no assurance of success.

35 U.S.C. 103(a) rejection

1. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-66 are rejected under 35 U.S.C. 103 (a) as being unpatentable over Lyons et al (Lyons) (US 6,998,391) in combination with Von Hoff et al. (Ann. Int. Med. 85(2) pages 237-45, 1976) in view of Beppu et al. (Beppu) (US 4,690,918).

The applied reference has a common inventor with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art only under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 103(a) might be overcome by: (1) a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not an invention "by another"; (2) a showing of a date of invention for the claimed subject matter of the application which corresponds to subject matter disclosed but not claimed in the reference, prior to the effective U.S. filing date of the reference under 37 CFR 1.131; or (3) an oath or declaration under 37 CFR 1.130 stating that the application and reference are currently owned by the same party and that the inventor named in

the application is the prior inventor under 35 U.S.C. 104, together with a terminal disclaimer in accordance with 37 CFR 1.321(c). This rejection might also be overcome by showing that the reference is disqualified under 35 U.S.C. 103(c) as prior art in a rejection under 35 U.S.C. 103(a). See MPEP § 706.02(l)(1) and § 706.02(l)(2).

Lyons teaches a method for treating cancer associated with abnormal activities of kinases comprising administering a DNA methylation inhibitor and a kinase inhibitor to a patient (abstract). Lyons discloses that the administration of said combination to the host is effective in retarding the onset or progression of the disease (col.8, lines 20-25). Lyons discloses that a DNA methylation inhibitor can reactivate certain genes which participate in the pathways of protein tyrosine kinase (col.8, lines 47-49) and co-administration of DNA methylation inhibitor with other inhibitors may be advantageous in the treatment of cancers (col.19, lines 30-35). Lyons discloses the treatment of cancers such as tumor, carcinoma, colon, breast cancer, leukemia (col.6, lines 58-63 and col.22, lines 35-40). Lyons discloses the detection of a cancer such as CML can be detected by counting of the concentration of BCR/Ab1 positive cells in bone marrow and/or peripheral blood (col.3, lines 60-64). Lyons discloses the administration of DNA methylation inhibitor intravenously (col.4, line 10); at a dose range between 1-100 mg/m^2 (col.4, lines 27-67). Lyons also discloses the IV administration of DNA methylation inhibitor decitabine (col.14, lines 42-65). Lyons reference is silent in disclosing a cytidine analog 5-aza-cytidine.

Von Hoff et al. teach the use and effectiveness of 5-azacytidine, the cytidine analog, in the treatment of acute myelogenous leukemeia (abstract).

Von Hoff et al. discloses the effectiveness of 5-azacytidine in childhood leukemia or during the induction phase (page 239, col. 2nd. under European Trials). Von Hoff et al. disclose that "5-azacytidine seems to be cell-cycle phase specific in that it is most toxic to cells in the S phase, especially at low concentrations" (page 238, first para.). Von Hoff et al. teach the administration of 5-azacytidine by intravenous and subcutaneous routes (page 239, first col. first para. lines 2-7). Von Hoff et al. also suggest the dosage of 5-azacytidine for intravenous administration in the ranges of 1.1- 633.0 mg/m^2 (page 239, table 1 and page 240, 2nd col. 2nd para.). Von Hoff et al. disclose the doses from 2 mg/m^2 –3.3 mg/m^2 per day and can be increased to 70 to 100 times the initial starting dose (pages 239, last para. through page 240, first para.). Von Hoff et al. further teach the combination therapy of acute myelogenous leukemia with 5-azacytidine with other agents (page 241, table 3). Von Hoff et al. suggest a need for future clinical studies for using 5-azacytidine alone and in combination with other agents in the treatment of acute myelogenous leukemia (page 244, first col. third. para.).

Lyons and Von Hoff et al. differs from the applicant's invention that the references does not provide the use of a histone deacetylase inhibitor in the treatment of cancer.

Beppu teaches the histone deacetylase inhibitor trichostatin A and/or trichostatin C for the treatment of tumor cells (abstract). Beppu discloses that said drug inhibits proliferation of tumor cells in human or animal (col.1, lines 26-27). Beppu discloses the daily doses in the range from 0.05 to 100 mg for an adult (col.3, line 63). Therefore it would be obvious to one skill in the art to use other histone deacetylase inhibitors such as depsipeptide or phenylbutyrate due to their inherent properties to inhibit the

proliferation of tumor cells. Beppu also discloses that said drug can be administered in the form of injection solutions or drip infusion formulations (col.3, lines 40-45).

With regard to detecting the level of EZH2 expression in *vivo* in the patient or a sample derived from the patient; an EZH2 antagonist; and anti-neoplastic agent, it would be within the scope of the artisan in this art to detect the level of EZH2 expression in *vivo* in the patient and use an EZH2 antagonist; and anti-neoplastic agent due to their inherent properties to inhibit cancer cells, through routine experimentation in the absence of unexpected results with a particular combination.

Therefore, one of ordinary skill in the art would have found the applicants claimed method for treating a patient having a disease associated with over expression of EZH2, comprising administering to the patient a therapeutically effective amount of a DNA methylation inhibitor, to have been obvious at the time the invention was made having the above cited references before him. Since Lyons discloses that a DNA methylation inhibitor such as decitabine can reactivate certain genes which participate in the pathways of protein tyrosine kinase and co-administration of DNA methylation inhibitor with other inhibitors may be advantageous in the treatment of cancers; Von Hoff et al. teach the use and effectiveness of a DNA methylation inhibitor 5-azacytidine, in the treatment of acute myelogenous leukemeia, and Beppu teaches the histone deacetylase inhibitor trichostatin A and/or trichostatin C for the treatment of tumor cells, one skilled in the art would have a reasonable expectation for success in combining the teachings of these references to accomplish the treatment of a disease associated with over-expression of EZH2 because a DNA methylation inhibitor alone or in combination

with other inhibitors such as a histone deacetylase inhibitor have shown activity against various cancers. The motivation for doing so is provided in the prior art, Lyons discloses that a DNA methylation inhibitor can reactivate certain genes which participate in the pathways of protein tyrosine kinase (col.8, lines 47-49) and co-administration of DNA methylation inhibitor with other inhibitors may be advantageous in the treatment of cancers (col.19, lines 30-35).

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Devesh Khare whose telephone number is (571)272-0653. The examiner can normally be reached on Monday to Friday from 8:00 to 4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anna Jiang, Supervisory Patent Examiner, Art Unit 1623 can be reached at (571)272-0627. The official fax phone numbers for the organization where this application or proceeding is assigned is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

dkhare

Devesh Khare, Ph.D.,J.D.
Art Unit 1623

November 29, 2006